

of fecal fat measurements and calorimetry experiments may not be sufficient to identify small differences between wild-type and knockout animals which over a period of time would be sufficient to explain the observed phenotype. Within these experimental limitations, the data presented herein demonstrate that $ERR\alpha$ mice are lean as a result of aberrant regulation of peripheral lipid mobilization. $ERR\alpha$ mice display a unique combination of properties that suggests that modulation of $ERR\alpha$ activity may provide an effective method to regulate fat metabolism and that $ERR\alpha$ would be a key drug target for the treatment of obesity and other disorders of fat deposition. In addition, the close linkage of *ESTRRA* and diabetes susceptibility locus IDDM4 (Sladek et al., 1997) together with physiological defects observed in *Estrra*^{-/-} mice suggests that drugs influencing $ERR\alpha$ activity could also be used to treat diabetes and other metabolic disorders.

In the Claims:

Please amend the following claims.

3. (Amended) The non-human transgenic animal of claim 1, wherein said animal is a mammal.
5. (Amended) The non-human transgenic animal of claim 1, displaying a lean phenotype.
6. (Amended) The non-human transgenic animal of claim 1, whose germ cells and somatic cells additionally comprise a transgene encoding a non endogenous $ERR\alpha$ orphan nuclear receptor gene, wherein said transgene is expressed at levels sufficient to complement the disrupted endogenous $ERR\alpha$ orphan nuclear receptor activity.
9. (Amended) A cell line derived from the non-human transgenic animal of claim 1.
15. (Amended) A method for screening and identifying a compound which modulates $ERR\alpha$ orphan nuclear receptor activity, the method including:
 - a) exposing the non-human transgenic animal of claim 5 to a candidate compound, and;

b) determining the activity of said ERR α orphan nuclear receptor in said animal, wherein an increase in the receptor activity as compared to an unexposed non-human animal is indicative of a compound being capable of increasing ERR α orphan nuclear receptor activity, while a decrease in said receptor activity as compared to an unexposed non-human animal, is indicative of a compound being capable of decreasing ERR α orphan nuclear receptor activity.

18. Method of identifying an agent which modulates fat and/or glucose metabolism *in vivo* comprising:

- a) providing a promoter operably linked to a selectable or assayable marker, said promoter being modulated by ERR α ;
- b) measuring or selecting for said marker in a presence and in an absence of an agent suspected of modulating the promoter modulating activity of ERR α , thereby identifying an agent which modulates ERR α activity wherein a difference in the transcriptional activity in the presence of said agent, as compared to that in the absence thereof, identifies said agent as a modulator of ERR α activity;
- c) administering said agent identified in b) to a non-human transgenic animal according to claim 1; and
- d) measuring lipid and/or glucose levels in said animal of step c) and comparing same with that of a control animal, not having been administered said agent, wherein a difference in lipid and/or glucose levels of the animal of step c) as compared to that of said control animal identifies said agent as a modulator of fat and/or glucose metabolism *in vivo*.

21. (Amended) The method of claim 20, wherein said mammal is a mouse.

22. (Amended) A modulator of fat and/or glucose metabolism *in vivo* identified by the method of claim 18.

23. (Amended) A method of modulating fat tissue growth and/or weight gain, comprising:

a) administering to an animal an agent which modulates the promoter activity of a gene, wherein said promoter comprises cis-acting elements selected from the group consisting of:

- i) an estrogen response element;
- ii) TGA AGG TCA;
- iii) AGG TCA NNN TGA CCT (SEQ ID NO:1); and
- iv) functional variants of i-iii)

such as to modulate the level of said gene, thereby modulating fat tissue growth and/or weight gain in said animal.

28. (Amended) A method of determining whether an agent modulates fat tissue growth and/or weight gain in an animal comprising:

a) providing a transcriptionally active preparation of $ERR\alpha$ or related factors and a DNA sequence comprising a promoter having a cis-acting sequence which modulates activity thereof by an interaction thereto of said $ERR\alpha$ and related factors;

b) measuring said transcriptional activity of said promoter or of a binding of at least $ERR\alpha$ or related factors to said cis-acting sequence in a presence and in an absence of an agent suspected of modulating the transcriptional activity of said promoter or the binding of said factors to said cis-acting sequence, thereby identifying an agent which modulates transcription of said promoter and wherein a difference in the transcriptional activity and/or binding in the presence of said agent, as compared to that in the absence thereof identifies said agent as a modulator of transcription;

c) administering said agent identified in b) to a non-human transgenic animal according to claim 1; and

d) measuring fat tissue growth and/or weight gain in the animal of step c) and comparing same with that of a control animal, not having been administered said agent, wherein a difference in fat tissue growth and/or weight gain of the animal of step c) as compared to that of the control animal identifies said agent as a modulator of fat tissue growth and/or weight gain *in vivo*.

32. (Amended) A modulator of fat and/or glucose metabolism *in vivo* identified by the method of claim 28.

33. (Amended) A method of treating and/or preventing obesity, comprising administering to an obese animal, or an animal susceptible of becoming obese, an agent which modulates the promoter activity of a promoter comprising a cis-acting element selected from the group consisting of:

- i) an estrogen response element;
- ii) TGA AGG TCA;
- iii) AGG TCA NNN TGA CCT (SEQ ID NO:1); and
- iv) functional variants of i-iii)

wherein cis-acting element is capable of binding to $ERR\alpha$

35. (Amended) A method of determining whether an agent modulates obesity in an animal comprising:

- a) providing a transcriptionally active preparation of $ERR\alpha$ or related factors and a DNA sequence comprising a promoter having a cis-acting sequence which modulates activity thereof by an interaction thereto of said $ERR\alpha$ and related factors;
- b) measuring said transcriptional activity of said promoter or of a binding of at least $ERR\alpha$ or related factors to said cis-acting sequence in a presence and in an absence of an agent suspected of modulating the transcriptional activity of said promoter or the binding of said factors to said cis-acting sequence, thereby identifying an agent which modulates transcription of said promoter and wherein a difference in the transcriptional activity and/or binding in the presence of said agent, as compared to that in the absence thereof identifies said agent as a modulator of transcription;
- c) administering said agent identified in b) to a non-human transgenic animal according to claim 1; and
- d) assessing obesity in the animal of step c) and comparing same with that of a control animal, not having been administered said agent, wherein a difference in obesity of the

animal of step c) as compared to that of the control animal identifies said agent as a modulator of obesity *in vivo*.

38. (Amended) The method of claim 37, wherein said mammal is a mouse.

39. (Amended) A modulator of glucose or fat metabolism *in vivo* identified by the method of claim 35.